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Lack of data drives uncertainty in PCB health risk assessments

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Abstract Health risk assessments generally involve many extrapolations: for example, from animals to humans or from high doses to lower doses. Health risk assessments for PCBs involve all the usual uncertainties, plus additional uncertainties due to the nature of PCBs as a dynamic, complex mixture. Environmental processes alter PCB mixtures after release into the environment, so that people are exposed to mixtures that might not resemble the mixtures where there are toxicity data. This paper discusses the evolution of understanding in assessments of the cancer and noncancer effects of PCBs. It identifies where a lack of data in the past contributed to significant uncertainty and where new data subsequently altered the prevailing understanding of the toxicity of PCB mixtures, either qualitatively or quantitatively. Finally, the paper identifies some uncertainties remaining for current PCB health assessments, particularly those that result from a lack of data on exposure through nursing or on effects from inhalation of PCBs.

Keywords PCBs · Hazard classification · Toxicity value · Uncertainty · Cancer · Partitioning · Transformation · Bioaccumulation

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Introduction

Health risk assessments generally involve many extrapolations, for example, from experimental animals to humans, from high doses to lower doses, from one exposure route to another, from short-term exposure to lifetime exposure, and from a healthy adult population to susceptible populations that include children. Each extrapolation introduces uncertainty in the risk assessment, as each extrapolation makes a plausible assumption to fill a lack of data. An assessment might assume, for example, that animal results apply equally to humans, that risk is proportional to total dose regardless of exposure scenario, or that children and adults are equally susceptible.

Health risk assessments for PCBs involve all the usual extrapolations and uncertainties, plus there are additional uncertainties due to the nature of PCBs as a dynamic, complex mixture. Environmental processes alter PCB mixtures after release into the environment, so that people can be exposed to mixtures that might not resemble the mixtures that were the subject of human observational studies or animal experiments.

This paper discusses the evolution of understanding in assessments of the cancer and noncancer effects of PCBs. It identifies where a lack of data in the past contributed to a significant uncertainty and where new data subsequently altered the prevailing understanding of the toxicity of PCB mixtures. These new data have improved our understanding of PCB toxicity and have led to updated health risk assessments where there is greater confidence.

Lack of data and uncertainty related to PCB exposure

PCBs are complex mixtures of up to 209 congeners that have varying physical, chemical, and toxicologic properties.

Related compounds—PCB metabolites, chlorinated dibenzofurans, and brominated or other mixed halogenated biphenyls—can also be present. In the environment, PCB mixtures are affected by multiple processes that alter their congener composition (U.S. EPA 1996; Cogliano 1998). Partitioning refers to the process by which different fractions of a PCB mixture separate into air, water, sediment, and soil, with different congeners having varying affinities for each environmental medium. Chemical transformation refers to processes that alter the PCB molecules themselves, through biodegradation or through other processes such as photolysis and hydrolysis. Bioaccumulation refers to processes through which PCBs, which are highly soluble in lipids, are absorbed by fish and other animals, then persistent congeners that prove resistant to metabolism and elimination are preferentially retained, so that concentrations of these congeners increase in animal species higher in the food chain. The combined effect of the environmental processes of partitioning, chemical transformation, and preferential bioaccumulation results in substantial uncertainty, as environmental exposures are generally to PCB mixtures that differ considerably from the original commercial products.

It has long been recognized that "the composition of PCBs in most environmental extracts does not resemble the composition of the commercial products" (Safe 1994). Virtually all early toxicity studies, however, investigated commercial PCB products marketed under the trade names Aroclor, Kanechlor, or Clophen. Occupational studies, too, generally involved workers who manufactured or used these commercial products. The lack of toxicity data on PCB mixtures found in the environment, and the consequential reliance on studies investigating commercial PCB products, has been a fundamental uncertainty in health risk assessments for PCBs in the general ambient environment.

The commercial products themselves can differ substantially. For example, there is virtually no overlap of congeners between Aroclors 1016 and 1260, the former composed of congeners with four or fewer chlorines and the latter composed of congeners with five or more chlorines (Silberhorn et al. 1990). This fact has promoted the development of hypotheses about the relative toxicity of different PCB mixtures. In the absence of data, some assessments treated all PCB mixtures similarly, while other assessments assumed that more highly chlorinated mixtures are more toxic. The lack of data on PCB mixtures of varying composition has been another fundamental uncertainty that has motivated investigators to conduct parallel investigations of multiple commercial products or other PCB mixtures, at least for a small number of health outcomes.

Even different lots of the same commercial product can vary in composition and toxicity. Perhaps, the most notable example is Aroclor 1254, which was manufactured through at least two different processes. All Aroclor 1254 samples should have a chlorine content of 54 %, yet substantial differences in congener composition and relative toxicity have been documented (Kodavanti et al. 2001). The lack of data on the extent and toxicologic implications of lot-to-lot differences has contributed to the uncertainty in estimating the health risks of PCBs.

PCBs and cancer

In the first lifetime animal study of PCBs, Kimbrough et al. (1975) reported hepatocellular carcinomas in female Sherman rats fed Aroclor 1260 for 21 months. This study, coupled with some previous shorter-term studies from the early 1970s showing precancerous lesions in rats and mice, raised concerns about the potential for PCBs to cause cancer. These new findings, coupled with information about the long-term environmental persistence of PCBs, led to their regulation. The USA banned the manufacture and import of PCBs in the 1970s under the then-new Toxic Substances Control Act of 1976. Most other industrialized countries did the same a few years before or after the ban in the USA. By the 1980s, most countries had banned the production and use of PCBs, although the International Agency for Research on Cancer has reported the recent production of PCBs in North Korea (Lauby-Secretan et al. 2013).

Subsequent lifetime animal studies confirmed the potential of mixtures with 54–60 % chlorine to cause cancer in male and Fischer 344 rats (NCI 1978) and in female Sprague-Dawley rats (Norback and Weltman 1985). In the first lifetime animal study to investigate multiple PCB mixtures in parallel, Clophen A 60 (about 60 % chlorine content) was more effective than Clophen A 30 (about 42 % chlorine content) in inducing hepatocellular carcinomas in male Wistar rats (Schaeffer et al. 1984). This finding was consistent with the results of two earlier shorter-duration studies of Kanechlor mixtures. In one of these studies, Kanechlor 500 (about 60 % chlorine) was most effective, followed by Kanechlors 400 and 300 (approximately 54 and 42 % chlorine, respectively), in inducing nodular hyperplasia in male Wistar rats fed these mixtures for up to 12 months (Ito et al. 1974). In the other study, Kanechlor 500, but not Kanechlors 400 and 300, induced hepatocellular carcinomas in dd mice fed the mixture for 8 months, though the group sizes were small and the results were not statistically significant (Ito et al. 1973). In 1994, the liver tumor diagnoses of these and other rat studies were re-evaluated using the diagnostic criteria and nomenclature of that time (Moore et al. 1994). This re-evaluation found that mixtures with 60 % chlorine consistently induced high incidences of liver tumors, while mixtures with 54 or 42 % chlorine showed no statistically significant increases.

During the 1980s and early 1990s, the relative lack of data on PCB mixtures with less than 54–60 % chlorine resulted in

considerable uncertainty about the carcinogenicity of less chlorinated mixtures. Some scientists regarded any PCB mixture as potentially carcinogenic, while others referred to a dichotomy of "carcinogenic PCBs" and "noncarcinogenic PCBs," with the division marked by a chlorine content somewhere below 54–60 %.

This uncertain dichotomy between carcinogenic PCBs (mixtures with 60 % chlorine) and noncarcinogenic PCBs (mixtures with lower chlorine content) lasted for several years until a new study provided strong evidence to assess and compare the carcinogenic potential of four Aroclor products with different congener profiles: Aroclor 1016, Aroclor 1242, Aroclor 1254, and Aroclor 1260. Statistically significant, dose-related, increased incidences of liver tumors were found for each mixture (Mayes et al. 1998). These new data were able to substantially reduce a prior uncertainty.

Human data accumulated slowly. The first IARC Monograph on PCBs found reports of nine cancer cases (3 stomach cancers, 1 liver cancer, 2 lung cancers, 1 breast cancer, and 2 lymphomas) among 22 deaths in Japan following the consumption in 1968 of rice oil accidentally contaminated with Kanechlor 400 and two melanoma cases reported in a letter to the editor among 31 workers heavily exposed to Aroclor 1254 (IARC 1978). IARC termed this evidence "suggestive" and noted that the rice-oil patients and the industrial workers had also been exposed to other chemical agents.

The first cohort studies, published in the 1980s, reported cancer in the liver, gall bladder, biliary tract, or gastrointestinal tract of capacitor manufacturing workers. These findings, positive in each study but not consistent across cancer sites, led IARC (1987) to classify the human evidence as "limited." In this evaluation, several uncertainties were noted: numbers of cases were small, dose-response relationships could not be evaluated, and the role of chemical compounds other than PCBs could not be excluded.

It was not until the 1990s that the human studies began to find more consistency across cancer sites. Still, as late as 2000, the most discussed target was the liver and biliary tract, perhaps because there was clear evidence in animals of hepatocellular carcinoma following exposure to a wide range of PCB mixtures (ATSDR 2000). More recently, a Working Group convened by IARC in 2013 found several studies, in the workplace and in the general population, showing excess risks of melanoma, constituting sufficient evidence in humans. There was also limited evidence in humans for breast cancer and for non-Hodgkin's lymphoma. In view of the epidemiologic evidence, supported by sufficient evidence in experimental animals and additional evidence of mechanistic events relevant to human carcinogenesis, IARC classified PCBs in group 1 as carcinogenic to humans (Lauby-Secretan et al. 2013; IARC 2015).

In their review, IARC identified several etiologic characteristics involved in PCB carcinogenesis. PCBs can induce formation of reactive oxygen species, are genotoxic, cause immune suppression, induce an inflammatory response, and modulate receptor-mediated effects. Dioxin-like congeners act primarily through activation of the aryl hydrocarbon (Ah) receptor and subsequent events, while lower-chlorinated congeners begin through metabolic activation (Lauby-Secretan et al. 2013). These constitute a majority of the key characteristics of carcinogens identified by Smith et al. (2015).

In a separate evaluation statement, IARC also classified a dozen dioxin-like PCB congeners in group 1 as carcinogenic to humans (Lauby-Secretan et al. 2013; IARC 2015). These dioxin-like congeners had been identified by expert panels convened by the World Health Organization (Ahlborg et al. 1994; Van den Berg et al. 2006). IARC based its classification on extensive evidence of an aryl hydrocarbon receptor-mediated mechanism identical to that of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, plus sufficient evidence of carcinogenicity in experimental animals. IARC noted that the carcinogenicity of PCBs cannot be attributed solely to the dioxin-like congeners.

Toxicity values for cancer

For cancer, the U.S. EPA generally derives an oral slope factor to estimate the slope of the dose-response curve at low doses. This slope factor can then be multiplied by a person's lifetime average daily dose to obtain a plausible upper bound on the increased cancer risk attributable to lifetime exposure. For example, if a person's lifetime average daily dose is 1×10^{-5} mg/kg-day and the slope factor is 2 per mg/kg-day, then a plausible upper bound on the lifetime cancer risk from this exposure is $(1\times10^{-5}$ mg/kg-day$)\times(2$ per mg/kg-day$)=2\times10^{-5}$ or 2 in 100,000.

Before 1996, the cancer potential of PCBs had been characterized by a single oral slope factor that was applied uniformly to all PCB mixtures. The past lack of data on different PCB mixtures introduced considerable uncertainty into health risk assessments, as PCB mixtures are not all alike and there was no accepted method to quantify differences in carcinogenic potential.

In 1996, the EPA was able to derive a set of oral slope factors based on the dose-response data in female rats for each Aroclor mixture tested in the Mayes study cited above (EPA 1996; Cogliano 1998). Table 1 shows that there is a 30-fold spread between the oral slope factors derived for the different mixtures: 2 per mg/kg-day for Aroclors 1260 and 1254, 0.4 per mg/kg-day for Aroclor 1242, and 0.07 mg/kg-day for Aroclor 1016, all rounded to one significant digit. The study information was published by Mayes in 1998, but the EPA was able to accelerate its development of toxicity values by using the underlying laboratory report (Brunner et al. 1996) that it had obtained 2 years earlier.

Table 1 Application of cancer slope factors for PCBs to various exposure pathways

Data source	Slope factor (per mg/kg-day)	Exposure pathways where the slope factor applies	Rationale
Highest risk and persistence			
Aroclor 1260 Aroclor 1254	2	Contaminated fish and other foods Sediment or soil ingestion Dust or aerosol inhalation	Congeners with high chlorine content tend to bioaccumulate and adsorb to sediments, soils, and dusts
Lower risk and persistence			
Aroclor 1242	0.4	Ingestion of water-soluble congeners Inhalation of volatilized congeners Dermal exposure	Congeners with low chlorine content tend to be more water-soluble or volatile For dermal exposure, because PCBs are incompletely absorbed through the skin. If an absorbed dose has been calculated to account for this, use the slope factor for high risk instead
Lowest risk and persistence			
Aroclor 1016	0.07	Congeners with >4 chlorines are <0.5 %	Aroclor 1016 generally has <1 % congeners with >4 chlorines

Sources: U.S. EPA (1996); Cogliano (1998)

EPA applies these three slope factors to PCB mixtures from different environmental pathways, after considering how partitioning, chemical transformation, and preferential bioaccumulation would likely alter a PCB mixture between release into the environment and human exposure. The highest slope factor, 2 per mg/kg-day derived from data on Aroclors 1260 and 1254, is used for exposure pathways where environmental processes would tend to increase risk: consuming PCBs that have bioaccumulated through the food chain or ingesting contaminated soils or sediments. The next slope factor, 0.4 per mg/kg-day derived from data on Aroclor 1242, is used for exposure pathways where environmental processes would tend to decrease risk: ingesting water-soluble congeners or inhaling volatilized congeners. The lowest slope factor, 0.07 per mg/kg-day derived from data on Aroclor 1016, is used for exposure pathways where a chemical analysis of the mixture demonstrates that the mixture is composed of congeners with no more than four chlorines (Aroclor 1016 was manufactured from Aroclor 1242 by removing congeners with more than four chlorines; the result is that congeners with more than four chlorines generally comprise less than 1 % of Aroclor 1016; see Silberhorn 1990). These uses of different slope factors for different exposure pathways are presented in Table 1.

The California Environmental Protection Agency develops Public Health Goals to provide information on health effects of contaminants in drinking water. They often develop original dose-response estimates for carcinogens present in the environment. Their assessment of PCBs in drinking water (California EPA 2007), however, adopted and used the U.S. EPA's slope factor of 0.4 per mg/kg-day, in accordance with the U.S. EPA's advice to use this value to estimate risks from ingestion of water-soluble PCB congeners (Table 1).

The World Health Organization has estimated the cancer potential of 12 dioxin-like PCB congeners whose effects are mediated through the aryl hydrocarbon receptor (Van den Berg et al. 2006). They did this by estimating toxic equivalency factors for each dioxin-like PCB congener, which measure potency as a fraction of the potency of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, the index chemical for agents that act through this mechanism. For example, the most potent PCB congener is PCB-126, which was assigned a TEF of 0.1, meaning that PCB-126 has approximately one tenth the potency of 2,3,7,8-TCDD for effects mediated through the aryl hydrocarbon receptor.

Lack of data and uncertainty related to cancer

Several uncertainties remain in these dose-response assessments:

- Selection of a slope factor for each exposure pathway allows health risk assessments to reflect the effect of environmental processes and provides a 30-fold range to represent PCB mixtures with higher or lower carcinogenic potential. Nonetheless, this is still a simplification of a highly complex system with many unknowns.
- Slope factors are derived from liver tumors in rats and might not reflect the risk of melanoma in humans, nor the presumed risks of breast cancer and non-Hodgkin's lymphoma found recently by IARC (Lauby-Secretan et al. 2013; IARC 2015).
- The toxicity of PCB-11 (3,3′-dichlorobiphenyl), a prevalent congener in indoor air that has not been detected in Aroclor mixtures, may not be adequately represented by that of Aroclor 1016, the tested PCB mixture with the lowest chlorine content.

Another set of uncertainties arises from the multiplicity of mechanisms through which PCBs operate. IARC identified several mechanistic events involved in carcinogenesis induced by different congeners (Lauby-Secretan et al. 2013; IARC 2015):

- Lower-chlorinated PCB congeners can be readily metabolized into highly reactive electrophilic species, which can produce DNA adducts and reactive oxygen species, and are directly genotoxic and mutagenic. These congeners and their reaction products can serve as initiating agents in the production of hepatocellular carcinoma.
- Other PCB congeners can activate numerous receptors. A dozen dioxin-like congeners have strong affinity for the aryl hydrocarbon receptor (Van den Berg et al. 2006); sustained receptor activation can lead to altered cell proliferation and other events, producing toxicity similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Other congeners can activate the constitutive androstane or pregnane xenobiotic receptors (CAR/PXR) and induce these effects through other mechanisms (Al-Salman and Plant 2012). Still other congeners target the endocrine system; monohydroxylated metabolites of PCB congeners can act as either estrogen agonists or antagonists (Jansen et al. 1993). In addition to cancer, this might have reproductive or other toxic consequences.
- Some PCB congeners can compromise the immune system. Some highly chlorinated congeners with strong affinity for the aryl hydrocarbon receptor are potent immunotoxicants (Silkworth and Grabstein 1982).
- Some lower-chlorinated and some higher-chlorinated PCB congeners are associated with chronic inflammatory responses (Hori et al. 1982).

Thus, different congeners can induce different mechanistic events. Multiple congeners can operate at different steps along the same mechanistic pathway, and the activity started by one group of congeners can be completed by another. The specific mechanistic interactions of any given PCB mixture remain uncertain.

PCBs and health outcomes other than cancer

The first reports of various adverse health outcomes of PCBs came during the 1970s and 1980s following the Yusho and Yu-Cheng incidents of PCB-contaminated rice oil in Japan (1968) and Taiwan (1979), respectively. These include liver toxicity, dermal and ocular effects, neurologic effects, developmental toxicity, endocrine effects, immunotoxicity, respiratory effects, and gastrointestinal effects (ATSDR 2000). Because the rice oil had been heated repeatedly, there was also significant exposure to polychlorinated dibenzofurans that had formed from the heated PCBs. The lack of human studies in cohorts exposed to PCBs without augmented concentrations of PCDFs resulted in considerable uncertainty about whether these effects could be attributed to PCBs.

By the 1980s, human studies in other populations around the world had reported strong associations between PCBs—without the presence of augmented PCDFs—and developmental neurotoxicity, developmental toxicity, and dermal and ocular effects (ATSDR 2000). The most studied set of health outcomes has been developmental neurotoxicity, with several cohort studies reporting adverse health outcomes in children whose mothers ate PCB-contaminated fish or who otherwise had high levels of PCBs. Further testing of the children at later ages showed continued effects many years after perinatal exposure. More limited associations had also been found for reproductive effects in females and males, for thyroid toxicity, and for immunotoxicity. Many of these populations had concurrent exposure to other chemical agents, again raising the question of whether the observed associations are causal.

Animal studies have been conducted to provide further evidence to either support or refute the possibility that an observed association is causal. Strong animal evidence has accumulated for developmental neurotoxicity (in monkeys, rats, and mice), developmental toxicity (in monkeys and to a lesser extent in rats and mice), reproductive toxicity (in rats, mice, mink, and monkeys), liver toxicity (rats and monkeys), dermal and ocular effects (in monkeys), thyroid toxicity (in rats), and immunotoxicity (monkeys, rats, mice, guinea pigs, and rabbits) (ATSDR 2000).

By 2000, ATSDR had identified strong human evidence for neurotoxicity and dermal/ocular effects, and strong animal evidence for neurotoxicity, reproductive toxicity, developmental toxicity, hepatotoxicity, and immunotoxicity (ATSDR 2000).

Toxicity values for health outcomes other than cancer

For health outcomes other than cancer, the U.S. EPA generally derives an oral reference dose to estimate an exposure level (including in susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. For PCBs, the EPA derived separate oral reference doses from studies of Aroclor 1254 and Aroclor 1016, intended to represent PCB mixtures with high chlorine content and low chlorine content, respectively (U.S. EPA 1992, 1994a). The EPA also attempted to derive an oral reference dose from studies of Aroclor 1248 (a commercial PCB product of intermediate chlorine content) but was not able to verify a dose without appreciable risk of adverse health effects because an infant monkey died with PCB intoxication at the lowest dose tested (0.03 mg/kg-day) (U.S. EPA 1994b). This is a case where a lack of animal data at low-to-intermediate doses resulted in substantial uncertainty that precluded derivation of a toxicity value for PCB mixtures that resemble Aroclor 1248.

In addition, the U.S. EPA generally derives an inhalation reference concentration to estimate an ambient air concentration that is likely to be without appreciable risk of adverse health effects over a lifetime. For this purpose, inhalation studies are generally preferred, although a validated toxicokinetic model can be used to extrapolate across exposure routes. For PCBs, there were no data suitable to estimate an inhalation reference concentration (U.S. EPA 1992, 1994a, b). This is a case where a lack of data represented an uncertainty so substantial that it precluded derivation of toxicity values for inhalation exposures.

Similarly, the ATSDR derives minimal risk levels to estimate quantities that are similar in concept and methodology to reference doses and reference concentrations derived at the U.S. EPA. The ATSDR derived minimal risk levels for chronic-duration and intermediate-duration oral exposures, based on studies in monkeys (ATSDR 2000). The ATSDR did not derive multiple levels for different PCB mixtures, presumably because humans are exposed to complex mixtures that differ from the commercial mixtures and because minimal risk levels are intended to be screening levels based on the most sensitive noncancer health effects. Like the U.S. EPA, the ATSDR found no data suitable to estimate minimal risk levels for inhalation exposures. They also found no way to develop a toxic equivalency approach, particularly for health outcomes that are not mediated through the aryl hydrocarbon receptor.

Table 2 presents a summary of these toxicity values for outcomes other than cancer.

Lack of data and uncertainty related to health outcomes other than cancer

During the 1990s, the underlying philosophy in deriving reference values or minimal risk levels had been to determine the highest experimental dose where there was no observed adverse effect and then to divide this dose by a series of uncertainty factors that represent human variation, different types of uncertainty, or differences between study conditions and human exposure conditions. For the PCB reference values in Table 2, the following considerations resulted in division by composite uncertainty factors of 100–300 to obtain the reference values:

- Human variation in biologic susceptibility
- Uncertainty in extrapolating from animals to humans
- Uncertainty in inferring chronic effect levels when the best studies are of subchronic exposure
- Uncertainty in inferring a no-observed-adverse-effect level when even the lowest dose shows adverse effects
- Uncertainty based on an inadequate database for some health outcomes

This suggests that new data can reduce uncertainty, particularly (a) research that defines the range of human variation, (b) new human studies that are suitable for deriving a reference value, (c) studies of lifetime exposure so there will be no uncertainty in extrapolating results from less-than-lifetime studies, (d) studies at lower exposure levels so that a no-observed-adverse-effect level can be determined, and (e) studies that cover all health effects of concern.

A look towards the future: continued reduction of data gaps and uncertainty

Health risk assessments of PCBs have improved with the availability of new studies, nonetheless, important data gaps remain. In addition to the outcome-specific uncertainties noted above, there are some areas where cross-cutting uncertainties could be reduced with new targeted research:

- The nursing pathway has not been explicitly addressed. When a young girl or woman is exposed to PCBs, lipid-soluble congeners can be stored until they are passed via

Table 2 Toxicity values for PCBs for health outcomes other than cancer

Data source	Health outcome	Toxicity value (mg/kg-day)	Source
Chronic oral exposure			
Aroclor 1254	Immunologic effects in adult rhesus monkeys	2×10^{-5}	ATSDR (2000)
Aroclor 1254	Immunologic, ocular, and dermal effects in adult rhesus monkeys	2×10^{-5}	U.S. EPA (1994a)
Aroclor 1016	Reduced birthweight in rhesus monkeys	7×10^{-5}	U.S. EPA (1992)
Intermediate-duration oral exposure (15–365 days)			
Mixture of PCB congeners present in human milk	Neurobehavioral alterations in infant monkeys	3×10^{-5}	ATSDR (2000)
Inhalation exposure			
None			

Sources: ATSDR (2000); U.S. EPA (1992, 1994a)

her milk to her infant. There are multiple aspects of this uncertainty: how the exposure profile in the infant relates to the complex exposure history of the mother and how the toxicity of PCBs may be different for exposures early in life. The lack of toxicity values that reflect the nursing pathway creates uncertainty in contemporary health risk assessments that seek to cover early postnatal exposure.

- There are no toxicity values for inhalation. Moreover, a mixture of PCB congeners that volatilizes prior to inhalation exposure is likely to be very different from the mixtures of PCB congeners that have been studied through dietary exposures in humans or animals. In addition, there are no toxicity values for PCB-11, a congener that is prevalent in indoor air (Hu et al. 2008; Rodenburg et al. 2010; Guo et al. 2014). The lack of inhalation studies for PCBs is a critical data need for assessments that attempt to estimate the health risks from inhaling PCBs (Lehmann et al. 2015).

Conclusion

The past four decades have repeatedly seen data gaps filled and the attendant uncertainty reduced by new studies that permit better assessments of human health risks. New experimental studies have responded to the past lack of health-outcome data on commercial PCB products of varying composition and on PCB mixtures resembling those found in the environment. For human studies, where health outcomes were first seen for PCBs accompanied by high levels of PCDFs, later studies investigated other populations exposed to much lower PCDF levels. Quantitative dose-response studies on multiple PCB mixtures have shown large differences in cancer potential; these were quickly followed by analyses that allow cancer assessments to choose an appropriate potency estimate for different PCB mixtures encountered through different exposure pathways. This improves on early assessments that had made a dichotomy between "carcinogenic PCBs" and "noncarcinogenic PCBs" or that had derived a single toxicity value to apply to all exposure circumstances.

Still, important data gaps remain, most notably for nursing infants and for inhaled PCBs. Much work also remains in improving our collective understanding of the mechanisms and interactions by which PCBs can cause the various adverse health outcomes observed in humans or predicted from animal studies. IARC (2015) recently reviewed and synthesized the information on the numerous mechanisms by which PCBs can cause cancer, and similar reviews of mechanisms for developmental neurotoxicity and for other important health outcomes would be timely. With the advent of new testing methods for obtaining mechanistic data, it is likely that our understanding of PCB toxicity will continue to increase.

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